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Is it the time to offer rituximab as a cost-benefit treatment for immunoglobulin A nephropathy? A short-review to current concepts

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ABSTRACT

Context: IgA nephropathy (IgAN) as an autoimmune disease is the most common cause of glomerulonephritis worldwide. Rituximab effectively depletes B cells and reduces serum levels of IgA1 antibodies. This paper aimed to review the potential benefit of rituximab used in clinical practice of IgAN patients.

Evidence Acquisitions: PubMed, EBSCO, Web of Science, directory of open access journals (DOAJ), EMBASE, and Google Scholar were searched for the keywords of IgA nephropathy, rituximab, B cell depletion and autoimmune diseases.

Results: Rituximab therapy improved in nephropathies and in recurrent IgAN in several studies. The mechanisms of rituximab therapy in IgAN are unknown. However, a direct effect of rituximab on podocytes by cytoskeleton stabilization is possible. Additionally a possible effect of rituximab on B cells in IgAN may lead to its beneficial impact.

Conclusions: This short-review demonstrates that rituximab therapy may be an effective treatment option in IgAN patients, particularly for histological signs of active inflammation. However, results of safety and efficacy of rituximab in IgAN are limited, and definitive conclusions will require further studies. Thus, multicenter clinical trials for safety and efficacy of rituximab therapy are necessary.

Short-Review

Implication for health policy/practice/research/medical education:
Several recently randomized clinical trials underline the substantial risk of side effects and the lack of proven efficacy with all kinds of immunosuppressive treatment including rituximab. In concordance, other studies observed a reduction of hematuria after RTX therapy.

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1. Context

IgA nephropathy (IgAN) is the most common of glomerulonephritis worldwide that may results to chronic kidney failure in one-third of affected individuals. A wide variety of drugs have attempted to reduce the high risk of kidney failure in these patients (1,2). IgAN frequently leads to progressive chronic kidney disease (CKD), thus it requires much attention to prevent or slow the course of disease. While there are some benefits to adding immunosuppressive agents to standard therapy in IgAN, several studies have questioned safety and efficacy of these agents (3-5). B cell depletion potentially offers a new therapy (5). Rituximab (RTX) is a monoclonal antibody that specifically recognizes a large extracellular loop in CD20 molecule of B cells (6,7) and leads to significant depletion of these cells (8,9). This is FDA approved for non-Hodgkin's B cell lymphomas (10). Recently

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RTX is being increasingly used in various autoimmune diseases (11,12). IgAN is an autoimmune disease, indicating that RTX may be helpful to reduce the deterioration in kidney function (4). There are only few studies available using RTX for the treatment of IgAN from ten years ago (3). Hence, the present short-review aimed to consider, the impact of RTX in IgAN.

2. Evidence Acquisitions

PubMed, EBSCO, directory of Open Access Journals (DOAJ), Google Scholar, Scopus and Web of Science were searched with key words as IgA nephropathy, chronic kidney disease, rituximab, B cell depletion, rituximab and autoimmune diseases. The primary studies search resulted in a total of 4630 articles (including duplicates).

2.1. Study selection

The first author initially excluded those studies which were related to other fields (e.g., lie telling). Article titles not clearly signaling the field of research were not excluded in this step. The initial screening were further screened on the following criteria: (*a*) published in English language, (*b*) related to rheumatology or nephrology, (*c*) based on original data. Articles were used to screen a thorough check of mentioned criteria. After this step, 23 articles were identified. The reference sections of these articles were screened by hand to double check for studies.

3. Results

3.1. General findings

The 23 literature included in our review involve a total population of 1214 participants (910 male, 304 female), being tested in 71 independent samples. Forty-one of the samples contain IgAN and mild to moderate CKD and 30 of the samples contain sever CKD.

3.2. Rituximab for improvement of renal function in IgAN

Improvements of renal function are in line with earlier results on RTX therapy in nephropathies and in recurrent IgAN (13-18). However, Sugiura et al (19) did not find any proteinuria reduction after single-dose rituximab in five non-nephrotic IgAN patients. This contradiction between these studies may be explained by the fact that the first mentioned studies evaluated patients with highly active inflammatory state, defined by the presence of crescent formation and/or endocapillary proliferation in renal biopsy, similar to the study by Chancharoenthana et al (16). Accordingly in the study by Lundberg et al (20), electron microscopic examination of the repeated renal biopsy 50 months after the rituximab therapy revealed the disappearance of subendothelial. Reduced immunofluorescence staining for IgA after treatment with rituximab was established by Chancharoenthana et al (16). The varying outcome in crescentic IgAN has been reported by Lv et al (21). This contradiction between these studies may be explained by the fact that initial plasma exchange may have further improved renal function in the investigation by Lundberg et al (20). The rationale behind these results, which has had favorable findings in some earlier reports on moderate to severe IgAN, is to rapidly delete circulating IgA-containing immune complexes (22).

3.3. The mechanisms of rituximab therapy in IgAN

The mechanisms of rituximab therapy in IgAN are unknown, but besides a direct effect on podocytes by cytoskeleton stabilization, there may also be a possible effect on B cells as described by Fornoni et al (23) and by a direct modulation of T cell activity (24). This could in part explain its beneficial effect in other nephrotic disorders with or without the presence of autoantibodies. Most of those reviewed studies have been performed in teenage patients, which may have a better prognosis (25). Reporting bias may have an influence on the number of cases showing benefits for new agents and also affected on our knowledge about the impact of unconventional therapeutic methods (26).

3.3 The cost-benefit of rituximab therapy in IgAN

Lundberg et al (20) provided only two repeated courses in patients with proteinuria <3.5 g/d and four courses of this drug in the heavily nephrotic peoples. Based on the findings of pharmacokinetic studies performed in nephropathy has been shown that proteinuria may have an effect on the half-life of rituximab (27). Several recently randomized clinical trials underline the substantial risk of side effects and the lack of proven efficacy with all kinds of immunosuppressive treatment, including RTX (B cell–depleting therapy). In concordance with this clinical trial, other studies observed a reduction of hematuria after RTX therapy (20, 28). New treatment approaches for RTX are currently under investigation and may give us the opportunity to interfere in the pathogenesis of IgAN and with possibly fewer side effects (29).

3.4. The safety of rituximab therapy in IgAN

Treatment with rituximab was well tolerated in Fiorentino et al (30) study population, with limited adverse events and side effects after RTX therapy. Despite the small proportion of studies, the absence of serious adverse events and a little significant side effects is suggestive of the safety of RTX therapy, contrary to what is reported in the several studies, where non-serious (chills, skin rash, fever) and serious adverse events (angioedema, Steven–Johnson syndrome, bronchospasm) have been described (30,31). Longer follow-ups and larger patients are necessitated to definitely establish whether treatment with rituximab does not increase the risk of opportunistic infections or malignancies when used as immunosuppression in second-line (30). Data from a remarkably large series of rituximab therapy in primary glomerular diseases (32) nephropathy (33), lymphoproliferative disorders (34) and autoimmune diseases (35) show that rituximab is safe.

4. Conclusion

In conclusion, this short-review of article demonstrates that B cell depletion therapy with rituximab may be an effective treatment option in IgAN patients and histological signs of active inflammation. Further follow-up may be necessary to evaluate the long-term safety and clinical outcome of rituximab therapy in IgAN. The pathogenesis of IgAN needs to be investigated in multicenter clinical trials and safety and efficacy of rituximab therapy should be further evaluated. Results of safety and efficacy of rituximab therapy in IgAN are limited, and definitive conclusions will require further studies.

Authors' contribution

MRT and JM contributed to the search of the data and preparing of manuscript equally. All authors read and signed the final paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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References

1. Xie L, Tan C, Fan J, Fu P, Tang Y, Tao Y, et al. Mycophenolic acid reverses IgA1 aberrant glycosylation through up-regulating Cosmc expression in IgA nephropathy. Int Urol Nephrol. 2013;45(2):571-9. doi: 10.1007/s11255-012-0313-y.
2. Qin W, Zhong X, Fan JM, Zhang YJ, Liu XR, Ma XY. External suppression causes the low expression of the Cosmc gene in IgA nephropathy. Nephrol Dial Transplant. 2008;23(5):1608-14. doi: 10.1093/ndt/gfm781.
3. Floege J. Glomerular disease: Rituximab therapy for IgA nephropathy. Nat Rev Nephrol. 2017;13(3):138-140. doi: 10.1038/nrneph.2016.188.
4. Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. J Am Soc Nephrol. 2017;28(4):1306-1313. doi: 10.1681/ASN.2016060640.
5. Lundberg S, Westergren E, Smolander J, Bruchfeld A. B cell-depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis. Clin Kidney J. 2017;10(1):20-6. doi: 10.1093/ckj/sfw106.
6. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. Am J Transplant. 2006;6(5 Pt 1):859-66. doi: 10.1111/j.1600-6143.2006.01288.x.
7. Du J, Wang H, Zhong C, Peng B, Zhang M, Li B, et al. Structural basis for recognition of CD20 by therapeutic antibody Rituximab. J Biol Chem. 2007;282(20):15073-80. DOI:10.1074/jbc.M701654200.
8. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994;83(2):435-45.
9. Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of Rituximab in autoimmune disease—the immune complex decoy hypothesis. Nat Clin Pract Rheumatol. 2007;3(2):86-95. doi: 10.1038/ncprheum0424.
10. Grillo-López AJ. Rituximab: an insider's historical perspective. Semin Oncol. 2000;27(6 Suppl 12):9-16.
11. Eisenberg R. Update on Rituximab. Ann Rheum Dis. 2005; 64(suppl.4):55–7. doi: 10.1136/ard.2005.042648.
12. Scheinfeld N. A reviewof Rituximab in cutaneous medicine. Dermatol Online J. 2006;12(1):3.
13. Ishiguro H, Hashimoto T, Akata M, Suzuki S, Azushima K, Kobayashi Y, et al. Rituximab treatment for adult purpura nephritis with nephrotic syndrome. Intern Med. 2013;52(10):1079-83. doi: 10.2169/internalmedicine.52.9325.
14. Pillebout E, Rocha F, Fardet L, Rybojad M, Verine J, Glotz D. Successful outcome using rituximab as the only immunomodulation in Henoch-Schonlein purpura: case report. Nephrol Dial Transplant. 2011;26(6):2044-6. doi: 10.1093/ndt/gfr137.

15. Pindi Sala T, Michot JM, Snanoudj R, Dollat M, Estève E, Marie B, et al. Successful outcome of a corticodependent Henoch-Schonlein purpura adult with rituximab. Case Rep Med. 2014;2014:619218. doi: 10.1155/2014/619218.
16. Chancharoenthana W, Townamchai N, Leelahavanichkul A, Wattanatorn S, Kanjanabuch T, Avihingsanon Y, et al. Rituximab for recurrent IgA nephropathy in kidney transplantation: A report of three cases and proposed mechanisms. Nephrology (Carlton). 2017;22(1):65-71. doi: 10.1111/nep.12722.
17. El-Husseini A, Ahmed A, Sabucedo A, Fabulo E. Refractory Henoch-Schonlein purpura: atypical aetiology and management. J Ren Care. 2013;39(2):77-81. doi: 10.1111/j.1755-6686.2013.12007.x.
18. Donnithorne KJ, Atkinson TP, Hinze CH, Nogueira JB, Saeed SA, Askenazi DJ, et al. Rituximab therapy for severe refractory chronic Henoch-Schonlein purpura. J Pediatr. 2009;155(1):136-9. doi: 10.1016/j.jpeds.2008.12.049.
19. Sugiura H, Takei T, Itabashi M, Tsukada M, Moriyama T, Kojima C, et al. Effect of single-dose rituximab on primary glomerular diseases. Nephron Clin Pract. 2011;117(2):c98-105. doi: 10.1159/000319656.
20. Lundberg S, Westergren E, Smolander J, Bruchfeld A. B cell-depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis. Clin Kidney J. 2017;10(1):20-6. doi: 10.1093/ckj/sfw106.
21. Lv J, Yang Y, Zhang H, Chen W, Pan X, Guo Z, et al. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. J Am Soc Nephrol. 2013;24(12):2118-25. doi: 10.1681/ASN.2012101017.
22. Shenoy M, Ognjanovic MV, Coulthard MG. Treating severe Henoch-Schönlein and IgA nephritis with plasmapheresis alone. Pediatr Nephrol. 2007;22(8):1167-71. doi: 10.1007/s00467-007-0498-y.
23. Fornoni A, Sageshima J, Wei C, Merscher-Gomez S, Aguillon-Prada R, Jauregui AN, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med. 2011;3(85):85ra46. doi: 10.1126/scitranslmed.3002231.
24. Kessel A, Rosner I, Toubi E. Rituximab: beyond simple B cell depletion. Clin Rev Allergy Immunol. 2008;34(1):74-9. doi: 10.1007/s12016-008-8074-1.
25. Coppo R, Andrulli S, Amore A, Gianoglio B, Conti G, Peruzzi L, et al. Predictors of outcome in Henoch-Schönlein nephritis in children and adults. Am J Kidney Dis. 2006;47(6):993-1003. doi: 10.1053/j.ajkd.2006.02.178.
26. Greenhall GH, Salama AD. What is new in the management of rapidly progressive glomerulonephritis? Clin Kidney J. 2015;8(2):143-50. doi: 10.1093/ckj/sfv008.
27. Fervenza FC, Abraham RS, Erickson SB, Irazabal MV, Eirin A, Specks U, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol. 2010;5(12):2188-98. doi: 10.2215/CJN.05080610.
28. Coppo R, Davin JC. The difficulty in considering modifiable pathology risk factors in children with IgA nephropathy: crescents and timing of renal biopsy. Pediatr Nephrol. 2015;30(2):189-92. doi: 10.1007/s00467-014-2954-9.
29. Yeo SC, Liew A, Barratt J. Emerging therapies in immunoglobulin A nephropathy. Nephrology (Carlton). 2015;20(11):788-800. doi: 10.1111/nep.12527.
30. Fiorentino M, Tondolo F, Bruno F, Infante B, Grandaliano G, Gesualdo L, et al. Treatment with rituximab in idiopathic membranous nephropathy. Clin Kidney J. 2016;9(6):788-793. doi: 10.1093/ckj/sfw091.
31. Waldman M, Austin HA. Treatment of idiopathic membranous nephropathy. J Am Soc Nephrol. 2012;23(10):1617-30. doi: 10.1681/ASN.2012010058.
32. Marasà M, Kopp JB. Monoclonal antibodies for podocytopathies: rationale and clinical responses. Nat Rev Nephrol. 2009;5(6):337-48. doi: 10.1038/nrneph.2009.70.
33. Bomback AS, Derebail VK, McGregor JG, Kshirsagar AV, Falk RJ, Nachman PH. Rituximab therapy for membranous nephropathy: a systematic review. Clin J Am Soc Nephrol. 2009;4(4):734-44. doi: 10.2215/CJN.05231008.
34. Winter MC, Hancock BW. Ten years of rituximab in NHL. Expert Opin Drug Saf. 2009;8(2):223-35. doi: 10.1517/14740330902750114.
35. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009;68(1):25-32. doi: 10.1136/ard.2007.083188.